SY 03-1 GENETIC BASIS OF BLOOD PRESSURE AND HYPERTENSION

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Human primary or essential hypertension is a complex, polygenic trait with some 50% contribution from genes and environment. Richard Lifton and colleagues provided elegant dissection of several rare Mendelian forms of hypertension, exemplified by the glucocorticoid remediable aldosteronism and Liddle’s syndrome. These discoveries illustrate that a single gene mutation can explain the entire pathogenesis of severe, early onset hypertension as well as dictating the best treatment.

The dissection of the much more common polygenic hypertension has proven much more difficult. Early studies used a single polymorphic marker such as the I/D polymorphism in the ACE gene and small numbers of cases and controls. Candidate gene studies have been largely non-informative and non-reproducible. These were followed by linkage studies, which used approximately 300 microsatellite markers distributed across the genome. These studies resulted in large peaks covering regions with 50–100 genes, with no easy way to quickly focus on a few genes of causal relevance. The real breakthrough came with the initiation of the genome wide association studies (GWAS) characterised by a much more thorough coverage of the genome with thousands single nucleotide polymorphisms (SNPs). Typically 500,000 – 2,500,000 SNPs have been used for the big, collaborative GWAS for hypertension. These studies resulted in several ‘hits’ or signals with a genome-wide significance and a high level of reproducibility between studies. These ‘hits’ have been used successfully to calculate genetic risk scores for cardiovascular complications such as left ventricular hypertrophy, stroke and coronary artery disease. Intragenic signals, such as for example Uromodulin, are being explored, imaging, histology as well as longitudinal health outcomes.

Precision medicine involves examining the genetic makeup of patients and their differing responses to drugs designed to treat specific diseases. By building up an understanding of the ‘strata’ of responses and the genetics of the diseases, we hope to create more personalised and effective forms of treatment for groups of patients most likely to benefit. Significant past investment in Scotland in electronic health records (EHRs) and translational medicine research, coupled with a vibrant healthcare technology industry, positions Scotland as the location to drive forward the precision medicine agenda globally.

References:

PATHOPHYSIOLOGIC SIGNIFICANCE OF NON-CODING RNA IN HYPERTENSION

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Genetic discovery in blood pressure is generally referenced in relation to protein-coding genes, despite the fact that genes less than 2% of the genome. Recent exploration of the DNA sequences between genes, once called ‘junk’ DNA, has revealed a wealth of transcripts for RNA species that do not encode protein. These non-coding RNAs (ncRNAs) have emerged as dynamic managers of the business of the genome, able to coordinate the expression of genes in time and space to achieve the complexities of normal development and growth. ncRNAs can also direct and influence the interaction between DNA and the environment that characterizes epigenetics. The diversity of structure and functions of ncRNAs is breathtaking and beyond their roles in normal biology, their roles in disease are beginning to take shape. Based on size, ncRNAs are classified as small (<200 nucleotides) or long that can range up to hundreds of thousands of nucleotides. Among the heterogeneous class of small ncRNA are the highly conserved miRNAs of about 22 nucleotides in length that exert post-transcriptional regulation of gene expression by repressing translation or degrading mRNA. The relationships between miRNAs and target genes is often promiscuous, reflecting the complex systems that link and coordinate genes with a common biochemical or physiological goal. Studies of miRNA in cardiovascular disease span more than 20 years. Associated with hypertension, a polymorphism in the angiotensin II type 1 receptor gene (AGTR1) known as A1166C in the 3’UTR region was found to alter the binding site for the miRNA miR-155, known to regulate the expression of AGTR1. However, the secrets of ncRNA are not always evident from DNA sequences and more often rely on expression data. The challenge here is the fact that the pathogenic expression of ncRNAs might be targeted to occur in certain tissues at certain times during development. Knowing where and when to sample tissue for expression analyses is daunting and often not feasible in man. However, recent studies in human kidneys have shown differential expression between hypertensive and normotensive subjects for a miRNA (miR-181a) that can bind and reduce nalsy gene expression. Interestingly, ncRNAs can be detected in the circulation and might provide a reflection of the expression in key tissues. Higher serum levels of miR-181a (that might be expected to reduce nalsy) have been correlated with increased systolic blood pressure. The findings would be consistent with a blood pressure-induced suppression of the nalsy-angiotensin system involving miR-181a. This emphasizes the potential complexity of dealing with the multisystem control of blood pressure and the homeostatic feedback loops in which ncRNAs might participate. The long ncRNA molecules (lncRNA) distinguish themselves through their ability to direct chromatin modification complexes to their sites of action, indicating that they are central to the epigenetic control of gene expression. They comprise the bulk of the human noncoding transcriptome and have their own complex biology, including some with actions as natural antisense transcripts (NATs). Best known in the cardiovascular world, the NAT called ANRIL was identified in the strongest genetic susceptibility locus for coronary artery disease in a gene desert on chromosome 9p21. Differentially expressed renal IncRNA and their target genes have been identified in Dahl and Spontaneously Hypertensive rats recently. Other IncRNA in vascular smooth muscle have been shown to be regulated by angiotensin II. However, the identification of IncRNA in human hypertension remains to be clarified. There is little doubt that we are on the threshold of understanding the genome in a much more sophisticated manner. The place of ncRNA in the biology of conditions such as hypertension hold enormous potential for both genetic and environmental investigation, prevention and treatment.

OVERVIEW OF SOMATIC MUTATIONS AND EPIGENETIC REGULATION OF ALDOSTERONE PRODUCING ADENOMA (APA)

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Primary aldosteronism (PA) is a heterogeneous group of disorders including both sporadic and familial forms (familial hyperaldosteronism type I, II and III). PA is the most frequent endocrine cause of secondary hypertension and associated with a higher rate of cardiovascular complications, compared with essential hypertension.

Here I review the recent progress in understanding of the genetic and molecular mechanisms leading to autonomous aldosterone production in PA.

Systematic screening detects primary aldosteronism in 5 to 10% of all patients with hypertension and in approximately 20% of patients with resistant hypertension. A unilateral APA is the most common curable cause of hypertension. Early detection of an APA is important both to cure of hypertension by means of adrenalectomy and to prevent the onset of resistant hypertension and the risk of long-term cardiovascular complications, such as left ventricular hypertrophy, coronary artery disease, myocardial infarction, heart failure, and atrial fibrillation.

Novel somatic mutations in APA

Recent advances in genome technology have allowed researchers to unravel part of the genetic abnormalities underlying the development of APA. Pathogenic mechanisms of APA by the somatic mutation are as follows.